conflicting results in open-label studies of the efficacy of anakinra in AS [1, 2], it is clear from both the studies that certain individuals respond to the drug for up to 24 weeks. In our three cases, the response was sustained for up to 30 months. It may be that patients with sustained response have a more IL-1-mediated disease than non-responders. Our cohort also had a 40% greater baseline CRP compared with the German cohort, indicating that higher serum markers of inflammation may be a predictor of response as has been suggested for anti-TNF response in AS [7]. Haibel et al. [2] reported that 21% of their cohort achieved ASAS40 response that is substantially greater than the reported placebo response of 5.1% in a previous AS anti-TNF study [8].

To summarize, we feel that the available data do not completely exclude a role for anakinra therapy in some cases of AS. It remains a strong possibility that the inflammation associated with AS may be amenable to IL-1 pathway modulation and it is possible that IL-1 blockade, either partially with anakinra or more completely with monoclonal antibodies, may have a role. Future trials will address these issues.

**Rheumatology key message**
- Anakinra may have prolonged efficacy in certain individuals with active ankylosing spondylitis.

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**Progressive multifocal leucoencephalopathy in a patient with systemic lupus erythematosus treated with rituximab**

Sir, Progressive multifocal leucoencephalopathy (PML) is a rare but usually fatal demyelinating disease of the brain caused by JC papovavirus (JCV). At least 50–75% of the adult population are seropositive for JCV. When JCV reactivation occurs, focal plaques develop in central nervous system white matter. Viral proliferation causes lysis of oligodendrocytes and therefore rapid demyelination [1]. Rituximab is a relatively novel therapy for systemic lupus erythematosus (SLE) and PML has not previously been reported in a patient with SLE treated with rituximab.

The patient was a 45-yr-old woman with SLE, who presented with blurred vision, loss of balance, difficulty in speaking and swallowing and weight loss increasing over 3 weeks. She had a 23-yr history of SLE characterized by photosensitivity, facial rash, alopecia, Raynauld’s syndrome, neutropenia, thrombocytopenia and raised titres of anti-nuclear, anti-Ro, anti-Sm and anti-ribonucleoprotein (RNP) antibodies. Anti-double-stranded deoxy-ribonucleic acid (dsDNA), Crithidia luciliae, anti-phospholipid antibody, lupus anti-coagulant and complement levels were normal.

In the past, she had been treated with corticosteroids, azathioprine and oral cyclophosphamide, which had failed to control her neutropenia. Three months after discontinuation of cyclophosphamide, because of bone marrow toxicity, she developed severe haemorrhagic cystitis, and a cystectomy and urostomy were performed. There was a 3-month delay between stopping cyclophosphamide and the development of haemorrhagic cystitis that was not compatible with drug-induced bladder toxicity. It is possible that primary infection or reactivation of JCV caused haemorrhagic cystitis, as has been reported with other papovaviruses [2]. Unfortunately, the diagnosis of JCV haemorrhagic cystitis was not suspected at the time of cystectomy in 1999 and immunohistochemical staining for BK virus (BKV) was not carried out.

When neutrophil counts were <0.5 × 10^9/l, the patient had developed pneumonia, and when prednisolone doses were ≥20 mg or higher, Herpes zoster reactivation occurred on three occasions. Between 2002 and 2005, she received two courses of rituximab, 375 mg/m^2 × 4 weeks, and a single treatment of rituximab, 375 mg/m^2. SLE went into remission within 1 month of rituximab treatment and prednisolone was discontinued. At the time of presentation with neurological symptoms, she had been off prednisolone for 1 year and SLE had been in remission.

Examination revealed dysarthria, nystagmus in all directions, pass-pointing, dysdiadochokinesis and an ataxic gait. Muscle power and tendon reflexes were normal, plantar responses down-going and sensation intact. Laboratory investigations revealed a low white cell count of 2.1 × 10^9/l, neutrophils 1.02 × 10^9/l and lymphocytes 0.71 × 10^9/l. Anti-CD19-positive B-cell counts were zero and CD3-positive lymphocytes were 10% (10% CD4 and 8% CD8). Magnetic resonance imaging (MRI) of the brain demonstrated three white matter lesions, one in each cerebellar peduncle and one in the brainstem (Fig. 1). Cerebrospinal fluid analysis revealed increased protein (51 mg/l).
and JCV polymerase chain reaction (PCR) was positive, consistent with a diagnosis of PML. She was treated with cidofovir, 5 mg/kg fortnightly, and intravenous immunoglobulin (IVIG), 0.5 g/kg monthly. B-cell counts recovered to 0.16% but neurological disease progressed, resulting in death from respiratory failure 4 months after presentation. Roche Pharmaceuticals were informed of the case and an FDA alert was issued on 18 December 2006, informing doctors of this and another case of PML in a patient treated with rituximab.

Many patients with SLE receive immunosuppressive therapies, but only 16 cases of PML have been reported in patients with SLE [3–8]. Although immunosuppression may lead to JCV reactivation, the correlation between immunological factors and JCV reactivation is poorly understood. Rituximab is a chimeric monoclonal antibody that depletes CD20-positive B lymphocytes. In contrast, natalizumab, a monoclonal antibody used in the treatment of multiple sclerosis (MS), has the opposite effect on peripheral B-cell counts to rituximab. It blocks α4β1-integrins in bone marrow and spleen, increasing peripheral B-lymphocyte counts and was associated with a 1/1000 incidence of PML in MS patients [1]. It is B-cell proliferation rather than depletion that is thought to facilitate JCV reactivation by transporting viruses latent in kidneys, bone marrow and B lymphocytes to the brain. Lymphoproliferative disorders are known to be an important risk factor for PML [9]. When rituximab is added to treatment regimens for lymphoreticular malignancies, it appears to delay the onset of PML [9]. This patient had a history of prolonged immunosuppressive therapy and recurrent viral reactivation and it is plausible that rituximab may have delayed the onset of PML in this case rather than precipitating it.

The most common disease currently associated with PML is acquired immunodeficiency syndrome (AIDS), but in this case, serum human immunodeficiency virus (HIV) antibody was negative. Low CD4 and CD8 counts predispose to persistent papovavirus viruria and may have played a role in the development of this patient’s haemorrhagic cystitis and later PML [10]. The aetiology of PML in this patient with SLE treated with rituximab remains uncertain. SLE-related immune system defects and prior disease-modifying anti-rheumatic drug (DMARD) therapy are more likely to have predisposed the development of PML than the treatment with rituximab.

**Rheumatology key message**

- Rituximab: friend or foe?

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